



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
University Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2015

---

## **The cerebellar nodulus: Perceptual and ocular processing of graviceptive input**

Tarnutzer, A A ; Wichmann, W ; Straumann, D ; Bockisch, C J

**Abstract:** Current concepts postulate a decisive role of the cerebellar nodulus in the processing of otolith input. We hypothesized that nodular lesions abolish otolith-perceptual integration, predicting alignment of perceived direction of earth vertical with the z-axis of the head and not with gravity. In an 80-year-old patient with acute heminodular infarction, the subjective visual vertical deviated contralesionally by -21.1° when the patient was upright. After subtracting this offset, perceived vertical closely matched the patient's head orientation when the patient was roll-tilted. Otolith-ocular reflexes remained normal. This is the first report on abolished earth verticality perception in heminodular stroke and underlines the importance of the nodulus in spatial orientation. *Ann Neurol* 2014.

DOI: <https://doi.org/10.1002/ana.24329>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-104972>

Journal Article

Accepted Version

Originally published at:

Tarnutzer, A A; Wichmann, W; Straumann, D; Bockisch, C J (2015). The cerebellar nodulus: Perceptual and ocular processing of graviceptive input. *Annals of Neurology*, 77(2):343-347.

DOI: <https://doi.org/10.1002/ana.24329>

## **The cerebellar nodulus – perceptual and ocular processing of graviceptive input**

Tarnutzer A.A., MD (1), Wichmann W., MD (2), Straumann D., MD (1), Bockisch C. J. (1,3,4), PhD.

(1) Dept. of Neurology, University Hospital Zurich, Switzerland

(2) Institute of Neuroradiology, University Hospital Zurich, Zurich, Switzerland

(3) Dept. of Otorhinolaryngology, University Hospital Zurich, Switzerland

(4) Dept. of Ophthalmology, University Hospital Zurich, Switzerland

Running head: earth-verticality perception in nodular stroke

### Statistics

word count for the abstract (limited to 100 words): 100

word count for the paper (excluding abstract, figures and legends) – max 1500: 1493

character count for the title (including spaces and punctuation, limit 80 characters incl. spaces): 79

character count of the running head (including spaces and punctuation): 46

number of figures (max 3): 3

number of references (max 20): 20

### Corresponding author:

Alexander A. Tarnutzer, MD. Department of Neurology, University Hospital Zurich,

Frauenklinikstr. 26, 8091 Zurich, Switzerland. Phone: +41 44 255 55 11, Fax: +41 44 255 43 80.

Email: [alexander.tarnutzer@access.uzh.ch](mailto:alexander.tarnutzer@access.uzh.ch)

### Acknowledgements

The authors thank Marco Penner for technical assistance.

Funding: Swiss National Science Foundation (grant number: 32003B\_130163/1), Berne, Switzerland; the Betty and David Koetser Foundation for Brain Research, Zurich, Switzerland; the Center of Integrative Human Physiology, University of Zurich, Switzerland; Bonizzi-Theler-Foundation, Zurich, Switzerland.

**ABSTRACT:**

Current concepts postulate a decisive role of the cerebellar nodulus in the processing of otolith input. We hypothesized that nodular lesions abolish otolith-perceptual integration, predicting alignment of perceived direction of earth-vertical with the z-axis of the head and not with gravity. In an 80-year-old patient with acute heminodular infarction, the subjective visual vertical (SVV) deviated contralesional by  $-21.1^{\circ}$  when upright. After subtracting this offset, perceived vertical closely matched the patient's head orientation when roll-tilted. Otolith-ocular reflexes remained normal. This is the first report on abolished earth-verticality perception in heminodular stroke and underlines the importance of the nodulus in spatial orientation.

## INTRODUCTION

The most caudal parts of the cerebellar vermis, i.e., the ventral part of lobule IX (uvula) and lobule X (nodulus) are part of the vestibulo-cerebellum. These structures are a coordination center for eye, head, and body motion in space. The nodulus and uvula receive dense projections from the vestibular nuclei.<sup>1</sup> Neurons in the nodulus and the ventral uvula play an important role in integrating semicircular canal (SCC) and otolith signals<sup>2</sup> and discriminating head tilt from translation.<sup>3</sup> Thus, for spatial orientation, the nodulus and uvula are essential in generating internal models to provide neural estimates of direction of gravity. Electrophysiologically, Purkinje cells in the caudal vermis show responses that reflect estimates of head-tilt relative to gravity.<sup>4</sup>

Behaviorally, internal estimates of gravity can be quantified by setting a line along the perceived vertical – the subjective visual vertical (SVV). While estimates are very accurate when upright, systematic physiological roll-angle dependent misestimations occur: roll over-compensation (“E-effect”) for small ( $<60^\circ$ ) and large ( $>120\text{-}135^\circ$ ) whole-body roll-tilt, roll under-compensation (“A-effect”) for medium-sized (range= $60\text{-}120^\circ$ ) angles.<sup>5</sup> While several sensory systems contribute to internal estimates of verticality, otolith input is considered the most important source, as these organs directly sense linear acceleration.<sup>5</sup> In view of the dense otolith and SCC projections to the caudal vermis, we predict an important role of the nodulus and uvula in integrating otolith input for verticality estimates. Consequently, for nodular lesions we predict disruption of this integration, resulting in verticality estimates that are relative to the head and not to gravity.

The ventral uvula and the nodulus control the duration and spatial orientation of the angular vestibulo-ocular reflex (aVOR).<sup>6</sup> This nystagmus is elicited by a sudden change in head-rotation velocity along an earth-vertical axis and dies away with a decay time-constant (dTc) of 10-20sec, outlasting the corresponding dTc measured in the vestibular nerve by a factor of 2-3. The prolongation of the vestibular response is provided by a neuronal network (*velocity-storage mechanism*).<sup>7</sup> When the head is reoriented with respect to gravity early in the post-rotatory nystagmus phase, the dTc of the horizontal aVOR is reduced (*tilt dumping*),<sup>6</sup> while the velocity

along an axis orthogonal to the plane defined by the previous rotation and tilt axes is increased, reflecting a reorientation of the eye-rotation axis towards the gravitational vector<sup>8</sup> and indicating resolution of the canal-otolith conflict caused by the head-tilt.<sup>9</sup> In humans, bilateral (but not unilateral)<sup>11</sup> lesions of the nodulus and uvula result in a loss of tilt dumping.<sup>10-12</sup>

Here we describe changes in otolith-perceptual and otolith-ocular responses after heminodular stroke.

## **CASE DESCRIPTION**

A 80-year-old male was admitted to the emergency department with a sudden-onset spinning sensation accompanied by gait imbalance and nausea. A detailed neuro-otological evaluation revealed right-beating spontaneous nystagmus, but no gaze-evoked nystagmus, periodic alternating nystagmus (PAN), vertical skew or head-tilt. Finger-to-noise and heel-to-chin pointing were accurate; the head-impulse test was normal. Speech was not dysarthric. Walking was broad-based and severely ataxic and he tended to fall to the left side. MRI demonstrated sub-acute ischemia in the right cerebellar heminodulus (Fig. 1). Treatment with rivaroxaban was initiated as atrial fibrillation was detected. Having recovered almost completely, he was discharged after six days.

## **METHODS**

Written informed consent was obtained. The protocol was approved by the local ethics committee and was in accordance with ethical standards laid down in the 2013 Declaration of Helsinki for research involving human subjects.

The SVV was used to assess internal estimates of verticality in upright and whole-body roll-tilted positions ( $\pm 45^\circ/\pm 90^\circ$ ). By turning a knob, the patient repetitively adjusted a luminous line along perceived direction of vertical (15sec time limit for each adjustment, see<sup>13</sup> for details). For comparison, SVV measurements in 11 healthy controls were obtained. The integrity of the velocity-

storage mechanism was assessed by measuring the dTc of the aVOR during and immediately after rightward/leftward yaw-axis rotation (constant-velocity=100°/s) with the scleral search-coil technique (Universal Trading Ventures Inc., Cleveland, USA).<sup>14</sup> To quantify tilt suppression, we roll-tilted the patient 2sec after stopping the turntable clockwise (CW) or counter-clockwise (CCW) by 30° and compared dTcs with those without roll-tilting. Video-oculography (VOG; Interacoustics, Assens, Denmark) was used to quantify saccades, smooth pursuit, spontaneous nystagmus, gaze-evoked nystagmus, positional nystagmus, head-shaking nystagmus and the head-impulse test (all six canals). Cervical and ocular vestibular-evoked myogenic potentials (VEMPs) were obtained. All data was analyzed in Matlab (The Mathworks Inc., Nantick, USA) with custom-written programs.

## RESULTS

VOG demonstrated right (average=6.2°/s) and up-beating (average=2.6°/s) spontaneous nystagmus, while no nystagmus on eccentric gaze and no PAN were noted. Pursuit was hampered by the spontaneous nystagmus, but was otherwise smooth. Saccades were metric and had normal latency and velocity. There was no head-shaking nystagmus. Apogeotropic horizontal nystagmus was noted when turning the head to either side in supine position. VEMPs showed borderline asymmetry-ratios (normal<30%) with larger responses on the left side (cervical VEMPs: asymmetry-ratio=30% at 100dB; ocular VEMPs: asymmetry-ratio=36%). The 3D-video-head-impulse test was normal. Fundus-photography demonstrated static binocular cyclorotation to the left, suggesting partial ocular-tilt reaction.

The SVV (on day 3 after symptom-onset) deviated CCW (i.e., contralesionally) by  $-26.9 \pm 3.3^\circ$  /  $-17.9 \pm 2.8^\circ$  (average $\pm$ 1SD; CW/CCW arrow rotations) when upright (Fig. 2A). Adjustment errors were larger when roll-tilted left-ear-down compared to right-ear-down. Relative to healthy controls (95%-confidence interval, Fig. 2A), these errors were markedly larger. At follow-up 12 weeks later, the SVV had partially recovered with errors of  $-13.3 \pm 2.8^\circ$  /  $-8.0 \pm 3.5^\circ$  when upright and reduced errors when roll-tilted (Fig. 2B).

Internal estimates of direction of gravity in our patient were altered in two ways: (1) due to the laterality of the lesion, otolith processing was imbalanced, yielding a contralesional SVV bias when upright; and (2) perceived vertical when roll-tilted strongly deviated towards the whole-body roll-tilted position. In order to estimate the global shift in verticality perception, we subtracted this offset when upright. Resulting estimates during the acute phase and on follow-up were compared with predicted adjustments along earth-vertical and body-longitudinal axes (Fig. 2C). Acutely, estimates closely matched the prediction for head-fixed adjustments; on follow-up estimates were in-between an earth-fixed frame and a head-fixed frame.

aVOR and tilt dumping: During yaw rotation, the horizontal aVOR dTc averaged ( $\pm 1$ SD)  $9.3 \pm 1.0$ sec/ $6.8 \pm 1.4$ sec (rightward/leftward rotations). Post-rotatory dTcs (without pitch/roll) were  $11.2$ sec/ $12.5$ sec. Roll-tilting the patient by  $30^\circ$  2sec after abruptly stopping the turntable reduced the average horizontal aVOR dTc to  $7.4$ sec/ $6.7$ sec. Compared to the decrease of the dTc to  $\approx 7$ sec in healthy humans,<sup>8, 15, 16</sup> this suggests normal tilt dumping (Fig. 3).

## DISCUSSION

For a better understanding of the physiology and pathophysiology of the cerebellar nodulus, lesion studies and electrophysiological stimulation studies in non-human primates remain the most important source of information. In humans, literature about nodular function is scarce due to the very low incidence of selective lesions. This is the first report demonstrating that, after acute heminodular stroke, the perception of earth-verticality remains aligned with the head in different roll-tilt positions. Both the SVV bias and the patient's tendency to fall when walking were contralesional. Our findings support the hypothesis of the nodulus being critical in the use of otolith input to allow accurate verticality perception. On follow-up 12 weeks later, partial recovery of otolith-input integration, as indicated by SVV adjustments falling in-between predictions for head-fixed and earth-fixed coordinate frames, paralleled clinical recovery, and likely indicate that central



compensation was not complete. Preserved tilt suppression in our patient acutely after heminodular stroke compares well with data from healthy controls<sup>8, 15, 16</sup> and patients with heminodular lesions.<sup>11</sup> The dissociation between impaired perceptual and preserved vestibulo-ocular motor responses in case of a heminodular lesion indicates that the remaining heminodulus is sufficient to trigger aVOR tilt-suppression. This hypothesis is supported by Moon,<sup>11</sup> reporting loss of aVOR tilt in 2/2 patients with bilateral nodular lesions and 0/2 patients with unilateral nodular lesions.

Previously, upbeat nystagmus was described for cerebellar stroke in the PICA territory,<sup>17</sup> however, whether this was specifically linked to nodular damage is not clear. Our case suggests that heminodular damage may result in upbeat nystagmus. Lack of PAN in our patient suggests that bilateral damage of the nodulus is required for this peculiar spontaneous nystagmus.<sup>11, 18-20</sup> At the same time, we propose that based on our case and on one case with heminodular stroke in the literature,<sup>11</sup> not only bilateral lesions of the nodulus<sup>6</sup> or combined bilateral uvulo-nodular lesions<sup>18</sup> result in direction-changing (apogeotropic) positional nystagmus, but that heminodular damage is sufficient to cause such position-dependent ocular motor instability. Both spontaneous horizontal nystagmus beating towards the lesioned side<sup>11</sup> and contralesional lateropulsion<sup>11</sup> were previously described and matched findings in our patient. Gaze holding, smooth pursuit, saccades and the head-impulse test were normal, consistent with previous reports, indicating intact ocular-motor vermis and floccular regions.<sup>11</sup>

In summary, we propose that heminodular stroke results in a dissociation between perceptual and vestibulo-ocular motor otolith-mediated responses: while the integration of the otolith signal for perceptual estimates of direction of gravity is lost, tilt dumping is preserved, suggesting that residual heminodular function is sufficient to generate this reflexive response. Additional ocular-motor abnormalities after heminodular stroke in humans include spontaneous ipsilesional nystagmus and direction-changing (apogeotropic) horizontal positional nystagmus, while PAN suggests bilateral damage of the nodulus.

## FIGURE LEGENDS

### *Figure 1:*

MR-images demonstrating the location (indicated by the solid arrows) and extension (being restricted to the right heminodulus with possible minor involvement of the upper pole of the right cerebellar tonsil) of the ischemic lesion in the axial (panel A, axial T2-weighted sequence, slice thickness: 4mm, in addition, high-resolution T2-weighted axial images of the cerebellum were obtained with a slice thickness of 0.5mm), sagittal (panel B, fluid-attenuated inversion recovery or FLAIR sequence, slice thickness: 0.9mm) and frontal (panel C, FLAIR sequence; slice thickness: 1mm) plane (diffusion restriction on axial DWI (slice thickness: 4mm) not shown). MR-images: courtesy of the Institute of Neuroradiology, University Hospital Zurich, Switzerland.

### *Figure 2:*

Average adjustment errors ( $\pm 1SD$ ) of perceived vertical (acute phase: panel A; follow-up: panel B) with results separately presented for trials with CW (grey filled circles interconnected by a solid black line) and CCW (grey filled squares interconnected by a dashed black line) arrow rotations and predictions for adjustments when the nodulus is damaged (panel C). Panels A and B: for comparison, the 95% confidence interval (CI) of 11 healthy human subjects (not age-matched,  $43.1 \pm 13.4$  years; average age  $\pm 1SD$ ) is shown in grey. Panel C: predicted verticality adjustments both in case of preserved (i.e., along the earth vertical axis  $\rightarrow$  earth-fixed frame; light-grey dashed line) and abolished (i.e., along the head longitudinal axis  $\rightarrow$  head-fixed frame, light-grey dashed-dotted line) integration of otolith input are compared with the experimental data from our patient in the acute phase (in black) and on follow-up (in dark-grey). Based on the assumption that the laterality of the lesion induces an additional bias of fixed size in all positions, this offset as determined in upright position (Fig. 2A) was subtracted from all positions. Acutely after right-sided heminodular stroke perceived vertical (black solid line for CW arrow rotations; black dashed line

for CCW arrow rotations) matched the prediction for a head-fixed frame closely. On follow-up, perceived vertical (dark-grey solid line for CW arrow rotations; dark-grey dashed line for CCW arrow rotations) was in-between a head-fixed frame and an earth-fixed frame, suggesting partial recovery of otolith-input integration after heminodular loss.

*Figure 3:*

Post-rotatory angular vestibulo-ocular reflex (aVOR) decay characteristics are compared for conditions with and without whole-body roll ( $30^\circ$  CW or CCW) two seconds after leftward turntable rotation was abruptly stopped, predicting shortening of the dTc after tilting (with reported values ranging around 7sec).<sup>16</sup> In this example, eye velocity values (circles, the velocity of individual slow phases) and fits (using an exponential decay function) are shown for both conditions with tilt dumping (grey dashed trace, CCW head roll by  $30^\circ$ ) and without (black solid line) after leftward turntable rotation. Noteworthy, the dTc was shortened considerably from 12.6sec to 7.1sec when the patient was roll-tilted, indicating preserved tilt dumping.

Study contribution of each author:

A.A.T.: drafted the manuscript, recorded and analyzed the data and conceived of the study. He also approved the final version of the manuscript

D.S.: conceived of the study and read and approved the final version of the manuscript

W.W.: interpreted the MR-findings and read and approved the final version of the manuscript

C.J.B.: recorded and analyzed the data, read and approved the final version of the manuscript

Conflict of interest: The authors declare no competing financial interests.

## References

1. Fushiki H, Barmack NH. Topography and reciprocal activity of cerebellar Purkinje cells in the uvula-nodulus modulated by vestibular stimulation. *J Neurophysiol.* 1997 Dec;78(6):3083-94.
2. Angelaki DE, Hess BJ. Inertial representation of angular motion in the vestibular system of rhesus monkeys. II. Otolith-controlled transformation that depends on an intact cerebellar nodulus. *J Neurophysiol.* 1995 May;73(5):1729-51.
3. Yakusheva TA, Shaikh AG, Green AM, Blazquez PM, Dickman JD, Angelaki DE. Purkinje cells in posterior cerebellar vermis encode motion in an inertial reference frame. *Neuron.* 2007 Jun 21;54(6):973-85.
4. Laurens J, Meng H, Angelaki DE. Neural representation of orientation relative to gravity in the macaque cerebellum. *Neuron.* 2013 Dec 18;80(6):1508-18.
5. Tarnutzer AA, Bockisch CJ, Straumann D, Olasagasti I. Gravity dependence of subjective visual vertical variability. *J Neurophysiol.* 2009 Sep;102(3):1657-71.
6. Sheliga BM, Yakushin SB, Silvers A, Raphan T, Cohen B. Control of spatial orientation of the angular vestibulo-ocular reflex by the nodulus and uvula of the vestibulocerebellum. *Ann N Y Acad Sci.* 1999 May 28;871:94-122.
7. Raphan T, Matsuo V, Cohen B. Velocity storage in the vestibulo-ocular reflex arc (VOR). *Exp Brain Res.* 1979 Apr 2;35(2):229-48.
8. Fetter M, Tweed D, Hermann W, Wohland-Braun B, Koenig E. The influence of head position and head reorientation on the axis of eye rotation and the vestibular time constant during postrotatory nystagmus. *Exp Brain Res.* 1992;91(1):121-8.
9. Laurens J, Angelaki DE. The functional significance of velocity storage and its dependence on gravity. *Exp Brain Res.* 2011 May;210(3-4):407-22.
10. Jeong HS, Oh JY, Kim JS, Kim J, Lee AY, Oh SY. Periodic alternating nystagmus in isolated nodular infarction. *Neurology.* 2007 Mar 20;68(12):956-7.

11. Moon IS, Kim JS, Choi KD, et al. Isolated nodular infarction. *Stroke*. 2009 Feb;40(2):487-91.
12. Wiest G, Deecke L, Trattinig S, Mueller C. Abolished tilt suppression of the vestibulo-ocular reflex caused by a selective uvulo-nodular lesion. *Neurology*. 1999 Jan 15;52(2):417-9.
13. Tarnutzer AA, Schuknecht B, Straumann D. Verticality perception in patients with lesions along the graviceptive pathways - Acute deficits and subsequent compensation. *SANP*. 2011;162(2):60-5.
14. Bergamin O, Zee DS, Roberts DC, Landau K, Lasker AG, Straumann D. Three-dimensional Hess screen test with binocular dual search coils in a three-field magnetic system. *Invest Ophthalmol Vis Sci*. 2001 Mar;42(3):660-7.
15. Hain TC, Zee DS, Maria BL. Tilt suppression of vestibulo-ocular reflex in patients with cerebellar lesions. *Acta Otolaryngol*. 1988 Jan-Feb;105(1-2):13-20.
16. Benson AJ, Bodin MA. Interaction of linear and angular accelerations on vestibular receptors in man. *Aerosp Med*. 1966 Feb;37(2):144-54.
17. Huh YE, Kim JS. Patterns of spontaneous and head-shaking nystagmus in cerebellar infarction: imaging correlations. *Brain*. 2011 Dec;134(Pt 12):3662-71.
18. Cohen B, John P, Yakushin SB, Buettner-Ennever J, Raphan T. The nodulus and uvula: source of cerebellar control of spatial orientation of the angular vestibulo-ocular reflex. *Ann N Y Acad Sci*. 2002 Dec;978:28-45.
19. Waespe W, Cohen B, Raphan T. Dynamic modification of the vestibulo-ocular reflex by the nodulus and uvula. *Science*. 1985 Apr 12;228(4696):199-202.
20. Wearne S, Raphan T, Cohen B. Control of spatial orientation of the angular vestibuloocular reflex by the nodulus and uvula. *J Neurophysiol*. 1998 May;79(5):2690-715.







